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|---|---|
| EPPERSON, JON D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1639 | |

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/987,456 | ZAUDERER ET AL. | |
| | Examiner | Art Unit | |
| | Jon D. Epperson | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *84-122 and 127-131* is/are pending in the application.

4a) Of the above claim(s) *85-87,98,100-102 and 104-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,88-97,99,103,107-122 and 127-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/13/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *24 May 2005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Request for Continued Examination (RCE)*

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/05 has been entered. Claims 84-122 and 127-131 were pending. No claims were added, canceled or amended. Therefore, claims 84-122 and 127-131 are currently pending. Claims 85-87, 98, 100-102 and 104-106 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Consequently, claims 84, 88-97, 99, 103, 107-122 and 127-131 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

### Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

### Outstanding Objections and/or Rejections

#### *Claim Rejections - 35 USC § 103*

3. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**)

and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the

medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules or fragments thereof with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule, or antigen-specific fragment thereof are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression

levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus "pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high

yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph

through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a

preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.

***Response***

4. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered including all exhibits and/or declarations (and are incorporated in their entirety herein

by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

**[1]** Applicants argue, "... the cited references do not teach or suggest the introduction of two expression libraries into eukaryotic host cells" (e.g., see 7/21/05 Response, pages 18-19).

**[2]** Applicants argue, "There is nothing in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested to one of ordinary skill in the art the desirability of combining these reference. While Rowlands describes the expression of a single, previously known and identified recombinant antibody using a *vaccinia* virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to introduce two expression libraries encoding immunoglobulin subunit polypeptides into eukaryotic cells. Furthermore, while Zauderer describes the introduction of a single expression library of tumor, cancer, or infected cell-specific antigens, there is no suggestion to one of ordinary skill in the art that this could be used in conjunction with the Rowlands method" (e.g., 7/21/05 Response, pages 19 and 20).

**[3]** Applicants argue, "Waterhouse does not even describe eukaryotic host cells ... there is nothing in Waterhouse to suggest to one of ordinary skill in the art to introduce two expression libraries into eukaryotic cells for selecting polynucleotides which encode an immunoglobulin molecule" (e.g., see 7/21/05 Response, pages 20-21).

**[4]** Applicants argue, "In support of Applicants' arguments, Applicants submit herewith as Exhibit B the Declaration under 35 C.F.R. § 1.132 of Dr. Maurice Zauderer ... [stating] there was no motivation or suggestion for one of ordinary skill in the art to combine Rowlands,

Zauderer, or Waterhouse to arrive at the claimed invention because: 1) Rowlands does not teach or suggest introduction of libraries into eukaryotic cells; 2) Zauderer does not teach or suggest introduction into eukaryotic host cells of two expression libraries that separately encode immunoglobulin heavy and light chains; and 3) Waterhouse describes phage display techniques, which one of ordinary skill in the art would not have considered as features that could be extrapolated to eukaryotic systems. See Exhibit B at Paragraph 15" (e.g., see 7/21/05 Response, page 21, middle paragraph; see also Exhibit B).

**[5]** Applicants argue, "One of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells ... Given these different vectors and the difference in prokaryotic versus eukaryotic host cells, one of ordinary skill would not have expected any selection methods described in Waterhouse to be useable with vectors that express in eukaryotic hosts because there would be different conditions required for the two systems" (e.g., 7/21/05 Response, page 22, middle paragraph; see also paragraph bridging pages 22 and 23).

**[6]** Applicants argue, "... one of ordinary skill in the art would not have expected from Zauderer, which discloses introduction of one library into eukaryotic host cells, and Rowlands, which discloses the expression of a previously identified and known antibody in eukaryotic host cells, that two separate libraries could be randomly introduced into eukaryotic host cells to efficiently form a plurality of immunoglobulin ... In further support of Applicants' arguments, Applicants submit herewith as Exhibit A the Declaration under 35 C.F.R. § 1.132 of Dr. Walter J. Storkus ... he was skeptical that the technology would work ... he did not expect that good

antibodies could be selected in eukaryotic cells because ... he thought that there would be limitations on the throughput for screening libraries expressed in eukaryotic cells, and because it was thought that random pairs of immunoglobulin heavy and light chains, when expressed, would not associate properly in the eukaryotic cytoplasm" (e.g., see 7/21/05 Response, pages 23 and 24; see also Exhibit B, especially at paragraph 9).

[7] Applicants argue, "Dr. Zauderer provides his opinion that there was a long-felt and unmet need for the technology of the claimed invention because of the drawbacks that are associated with the two prevalent technologies for selecting human antibodies. Exhibit B at Paragraphs 16-17. This long felt need is evidenced by the strategic alliances hat have been formed between Vaccinex, Inc., exclusive licensee of the present invention, and several other companies that are interested in using the claimed invention" (e.g., see 7/21/05 Response, pages 24 and 25; see also Exhibit B, especially at paragraphs 16 and 17).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Applicants have already acknowledged that the combined references teach the use of two libraries (e.g., see 7/21/05 Response, page 19, paragraph 1, "Waterhouse discloses the introduction ... vectors encoding immunoglobulin heavy and light chain variable region fragments ... and suggests that the system can be used to generate large combinatorial libraries by providing repertories of heavy [i.e., library number 1] and light chain [i.e., library number 2] fragments"; see also 7/21/05 response, page 20, last paragraph, "... Waterhouse may suggest the introduction of separate repertoires of heavy [i.e., library number 1] and light [i.e., library number 2] chain variable region fragments [i.e., Waterhouse discloses two libraries]").

**[2]** In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B"

(i.e., producing two libraries simultaneously). Furthermore, in response to applicant's arguments against the Rowlands reference individually (or in combination with Zauderer), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

**[3]** The Examiner respectfully disagrees. A person of skill in the art (most likely a Ph.D.) working in the field of immunology and/or combinatorial chemistry (i.e., for the purpose of producing antibody and/or antibody libraries) would look to all relevant papers for guidance (e.g., papers encompassing phage display, vaccinia virus, etc.) because the problems encountered are not "unique" to any one system. The advantages obtained from producing large "primary" libraries of heavy and light chains (i.e., two libraries) and the advantages associated with being able to co-select these heavy and light chains in order to produce, for example, antibodies with high affinity are just as applicable to mammalian expression systems as they are to phage display. The products in each case (i.e., the antibodies or antibody libraries) would be the same. Furthermore, Applicants' own specification makes clear that a person of skill in the art would routinely look at a wide variety of expression systems for guidance (e.g., see specification, page 2 and 3, "Previously, three general strategies have been employed to produce immunoglobulin molecules ... In one approach, rodent antibody sequences have been converted into human antibody sequences, by grafting ... An alternative approach, which does not suffer this same limitation, is to screen recombinant human antibody fragments displayed on bacteriophage"). Thus, Applicants' arguments for a per se rule that a person of skill in the art would never combine the teachings of a "phage display" reference with a "vaccinia virus" reference even if

both references teach a method for producing antibodies is not persuasive. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Furthermore, in response to applicant's arguments against the Waterhouse et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

**[4]** The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 84, 88-97, 99, 103, 107-122 and 127-131 based upon 35 U.S.C. 103(a) as set forth above because:

"In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." (e.g., see MPEP § 716.01(c)). Here, Applicants provide no factual evidence. The interest of the expert in the outcome is great (i.e., it's the expert's application at issue). The opposing evidence is strong for the reasons stated in the newly amended rejection above. Finally, the nature of the matter, which Applicants are trying to establish, pertain only to legal conclusions (e.g., no motivation to combine, no reasonable expectation of success, etc.) that have been set forth in an entirely conclusory manner and thus should be afforded little or no weight (e.g., see *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's

opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"). In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

For example, Dr. Zauderer states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. For example, the claimed invention requires expression of an antibody library using a poxvirus. The Zauderer et al. reference (WO 00/28016), which teaches the expression of protein libraries using a poxvirus, was published on May 18, 2000. There is no evidence that anyone was working on a method to express fully functional antibodies in mammalian cells using the Zauderer et al. reference. Furthermore, even if such evidence did exist, *assuming arguendo*, it would not constitute a long felt need as this paper was published fairly recently. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited reference; they would still be unable to solve the problem. See MPEP § 716.04.

Furthermore, Applicants' arguments are not commensurate in scope with the claimed invention. The Declaration refers only to the system described in the above referenced application and not to the individual claims of the application. As such the declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. For example, Dr. Zauderer states, "no useful antibodies can be selected in immunoglobulin transgenic animals ... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target antigen ... the present invention overcomes these problems (e.g., see Zauderer Declaration, paragraphs 8-

10). However, Applicants have already made clear that the claimed invention is not limited to an "efficient" method for the production of "useful" antibodies. Thus, there was no long felt need to produce antibodies (or fragments thereof) with low binding affinity and/or specificity as these goals were readily obtainable by other means (e.g., see Zauderer Declaration, paragraph 9, "... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target", which implies that sometimes it does recognize the target, which obviates Applicants' long felt need argument; see also Zauderer Declaration, paragraph 8, "In some cases ... no useful antibodies can be selected in immunoglobulin transgenic animals", which implies that in other cases usefully antibodies can be obtained, which again obviates Applicants' long felt need argument). That is, Applicants' claims are not limited to an "efficient" method that produces antibodies with a high degree of selectivity and/or affinity. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Furthermore, in response to applicant's arguments against the Rowlands reference individually (i.e., with regard to point 1), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Likewise, in response to applicant's arguments against the Zauderer reference individually (i.e., with regard to point 2), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *Id.* Moreover, in response to applicant's arguments against the Waterhouse et al. reference

individually (i.e., with regard to point 3), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *Id.*

**[5]** The Examiner respectfully disagrees. Obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, Rowlands et al. teach a method for producing antibodies in vaccinia infected "mammalian" cells (e.g., see Rowlands et al. page 4, paragraph 2; see also paragraph bridging pages 7-8). Thus, the conclusion that a person of skill in the art would know how to express an antibody in a "mammalian" cell is reasonable. Zauderer et al. teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Thus, the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable. The Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow limited to expressing only one particular class of proteins (i.e., everything but Applicants' claimed antibodies). Furthermore, the prokaryotic/eukaryotic distinctions to which Applicants refer (e.g., see 7/21/05 Response, paragraph bridging pages 22 and 23) are not at issue in this case. The Waterhouse et al. reference is not being relied upon for the purpose to which Applicants allude. The Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction

conditions in some sort of hybrid expression system. The Waterhouse et al. reference is simply being relied upon to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. Thus, Applicants' arguments are moot.

**[6]** The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 84, 88-97, 99, 103, 107-122 and 127-131 based upon 35 U.S.C. 103(a) as set forth above because:

Applicants' arguments are not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716.02(d). The claims do not require "efficient" introduction of libraries into hosts cells or the production of "good" antibodies as Dr. Storkus contends. In fact, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination [which are included within the scope of Applicants' invention] cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular

recombination ... [however] the specification does not say that they cannot be used"). Furthermore, there is no requirement that the antibodies "associate properly in the cytoplasm" (e.g., see claim 84 wherein the polypeptides only need be "capable of" combining together) and any underlying facts to support this contention, which have not bee set forth by Dr. Storkus, have been refuted by the combined teachings of Rowlands et al., Zauderer et al. and Waterhouse et al., which clearly sets forth successful examples of the proper association of heavy and light chains (e.g., see page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). In fact, Applicants' go so far as to state that only "two" antibodies need be produced by the claimed method, which clearly does not constitute a useful screen (e.g., see 12/7/04 Response, page 24, "... claim 84 ... requires expression of a 'plurality' of different immunoglobulins, i.e., two or more different immunoglobulins" see also footnote 3 on page 24) (emphasis added). In addition, Applicants' claims are not even limited to antibodies. For example, claim 84 states that the polypeptides merely must be "capable" of combining and that "fragments thereof" may be screened. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

**[7]** The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 84, 88-97, 99, 103, 107-122 and 127-131 based upon 35 U.S.C. 103(a) as set forth above because:

Applicants' arguments are not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716). In the present case, Dr. Zauderer states, "The transgenic animal technology ... tends to produce antibodies that do not have useful activity. Phage display technology ... results in antibodies that, once removed from the context of the fusion protein, lose the ability to specifically recognize target antigen [which are limitations that are presumably overcome by the claimed invention]" (e.g., see Dr. Zauderer's Declaration, paragraph 16). However, "antibodies" with "useful" activity that recognize a specific target protein are not required by the claims. In fact, Applicants make clear that low efficiency methods that generate poor antibodies also fall within the scope of Applicants' claims (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination ... [however] the specification does not say that they cannot be used"). In fact, Applicants' go so far as to state that only "two" antibodies need be produced by the claimed method, which clearly would not lead to an antibody with a "useful" activity or even one that binds to a target molecule (e.g., see

12/7/04 Response, page 24, "... claim 84 ... requires expression of a 'plurality' of different immunoglobulins, i.e., two or more different immunoglobulins") (emphasis added). For example, Exhibit B3, sets forth, "Vaccinex's innovative library-based antibody discovery technology ... will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult [i.e., not impossible] to identify with other systems." Thus, Exhibit B3 makes clear that Applicants' licensees are only bargaining for Vaccinex's "efficient" methods for producing library-based antibodies, which is not commensurate in scope with the current claims. In addition, Applicants' claims are not even limited to antibodies. For example, claim 84 states that the polypeptides merely must be "capable" of combining and that "fragments thereof" may be screened.

Exhibits B2-B4 only serve to highlight this deficiency. For example, Exhibit B2 sets forth, "Vaccinex's technology offers the potential to directly generate fully functional antibodies against difficult targets such as homologous proteins and multi-pass membrane receptors" and Gilles Alberici, CEO of OPi, is quoted as saying, "We are excited about this collaboration with Vaccinex ... Vaccinex's innovative antibody discovery technology will enable use to make a technological leap to develop new fully human antibodies aiming at treating haematological diseases" (e.g., see Exhibit B2, page 1 of 2). However, the Examiner notes that the claims are not limited to "fully functional antibodies" (e.g., see above wherein Applicants' claims, for example, read on "fragments" thereof). In addition, Applicants claims are not limited to antibodies that bind "difficult targets" for treating haematological diseases. In addition, Applicants' claims are not limited to antibodies with "useful" activity or even to antibodies that bind to a target molecule at all (e.g., see 12/7/04 Response, page 24, "... claim 84 ... requires

expression of a 'plurality' of different immunoglobulins, i.e., two or more different immunoglobulins"; see also footnote 3 on page 24). Likewise, Exhibit B3 sets forth, "Vaccinex's innovative library-based antibody discovery technology ... will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult to identify by other systems." Again, Applicants' claims are not limited to "high quality, fully functional human monoclonal antibodies" (e.g., see above). Furthermore, Exhibit B4 sets forth, "The collaboration combined Vaccinex's capabilities to discover fully human monoclonal antibodies using its proprietary antibody discovery technology ... Vaccinex ... has developed the only library-based antibody discovery platform capable of directly expressing bivalent, fully human antibodies in mammalian cells." Again, Applicants' claims are not limited to "bivalent, monoclonal fully human antibodies" (e.g., see above). In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

In addition, Applicants have not established a nexus between the claimed invention and the licenses (e.g., see *In re GPAC Inc.* (CAFC) 35 USPQ2d 1116 (6/20/1995), "Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.' Stratoflex, 713 F.2d at 1539, 218 USPQ at 879; see Demaco, 851 F.2d at 1392, 7 USPQ2d at 1226."). For example, Exhibits B2-B4 do not mention the use of a vaccinia virus (e.g., claim 88), an MOI ranging from about 1 to about 10

(e.g., claim 99), a v7.5/tk virus genome (e.g., claim 107), etc. Thus, it is not clear whether the expression systems to which exhibits B2-B4 refer represent the currently claimed methods.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

***Double Patenting***

5. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) (i.e., Application No. 10/052,942) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to

said antigens, etc). The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach

"extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of "intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Applicants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition, Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Furthermore, Rowland et al. teach that "extracellular" screening can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used). Finally, a person of skill in the art would

have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response***

6. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "... that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '402 publication. At that time, Applicants will consider filing a terminal disclaimer" (e.g., see 7/21/05 Response, page 25).

This is not found persuasive for the following reasons:

The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection *should continue to be made by the examiner* in each application as long as there are conflicting

claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications.").

Accordingly, the double patenting rejection cited above is hereby maintained.

***Conclusion***

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 19, 2005

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